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Application No.: 10/774,802 Docket No.: 28967/34891.1

REMARKS

Restriction Requirement

In the restriction requirement, the examiner required the election of one of the sixty-five (13 x 5) allegedly patentably distinct inventions:

Group I: Claims 43-48, drawn to a method of inhibiting Flt4 receptor tyrosine kinase function in a mammalian organism with a neoplastic disease comprising administering an inhibitor of the binding of a Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells;

Group II: Claims 49-52, drawn to a method for antagonizing the function of Flt4 receptor tyrosine kinase in an organism comprising administering a polypeptide and a pharmaceutically acceptable carrier;

Group III: Claims 53, 55, and 58-60 (in part), drawn to a method of inhibiting neoplastic cell growth in a mammalian subject;

Group IV: Claims 54-55 (in part), 56-57, 58-60 (in part), drawn to a method of inhibiting neoplastic cell growth in a mammalian subject;

Group V: Claims 61-64, drawn to a method for treating a mammal having breast cancer comprising administering an inhibitor of the binding of a Flt4 ligand protein to Flt4 expressed in cells;

Group IV: Claims 65-70 and 77, drawn to a method for treating a neoplastic disorder comprising screening a mammalian subject to identify a neoplastic disorder and comprising a composition to a mammalian organism;

Group VII: Claims 71-72 and 74-76, drawn to a method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism;

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Group VIII: Claims 73-76, drawn to a method of inhibiting proliferation of blood vessel endothelial cells in a human organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells;

Group IX: Claims 78-80, drawn to a method of inhibiting proliferation of endothelial cells in a human organism having a breast carcinoma characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells;

Group X: Claims 81-84, drawn to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels;

Group XI: Claims 85-88, drawn to a method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism;

Group XII: Claims 89-90, drawn to a method of inhibiting neoplastic cell growth in a human subject; and

Group XIII: Claims 91-93, drawn to a method of inhibiting neoplastic cell growth in a mammalian subject.

The examiner further indicated that upon election of one of the above-mentioned groups, election of one of the following allegedly patentably sub-inventions is also required:

(A) an anti-Flt4 antibody, or a polypeptide comprising an antigen binding fragment thereof;

(B) an anti-VEGF-C antibody, or a polypeptide comprising an antigen binding fragment thereof;

(C) an anti-VEGF-D antibody, or a polypeptide comprising an antigen binding fragment thereof;

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(D) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C; and

(E) a polypeptide comprising a Flt4 binding fragment of human prepro-VEGF-C or human propro-VEGF-D conjugated to an antineoplastic agent.

Election

In response to the restriction requirement, applicants hereby provisionally elect Group X (claims 81-84, drawn to a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels), and "sub-invention" D (directed to a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and fragment are capable of binding to human VEGF-C), for continued examination ***with traverse***.

Traversal

A. Review of the PTO's standard and purposes for restriction

The Patent statute only permits restriction of independent and distinct inventions (35 USC 121), which the Patent Office interprets to permit restriction of independent "or" distinct inventions. (MPEP 803, Part I) But such restriction is proper only if there would be a "serious burden" on the examiner in the absence of the restriction. (MPEP 803; 808.02)There is no harm whatsoever in examining multiple independent or distinct inventions in one application. (MPEP 805)

Importantly, the MPEP contains numerous cautions to the effect that restriction practice is not merely a burden-easing tool to be used by examiners when examiners see fit to do so. For example, Section 803 ("Restriction – When Proper") states, "an application may properly be restricted to one of two or more claimed inventions only if they are able to support separate patents and they are either independent or distinct." Section 803.01 states, in all capital letters, "IT STILL REMAINS IMPORTANT FROM THE STANDPOINT OF THE PUBLIC INTEREST THAT NO REQUIREMENTS BE MADE WHICH MIGHT RESULT IN THE ISSUANCE OF TWO PATENTS FOR THE SAME INVENTION." Similarly, Section 804.01 states, "This apparent nullification of double

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patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention." Where inventions are related as disclosed but are not distinct as claimed, restriction is never proper. (MPEP 806; MPEP 808.02) "[I]t is imperative the requirement should never be made where related inventions as claimed are not distinct." (Id.)

In view of the foregoing, the MPEP instructs that "Examiners must provide reasons and/or examples to support conclusions . . . ." (MPEP 803, Part II) See also MPEP 808.01 ("The particular reasons relied on by the examiner for holding that the inventions as claimed are either independent or distinct should be concisely stated. A mere statement of conclusion is inadequate. The reasons upon which the conclusion is based should be given. For example, relative to a combination and a subcombination thereof, the examiner should point out the reasons why he or she considers the subcombination to have utility by itself or in other combinations, and why he or she considers that the combination as claimed does not require the particulars of the subcombination as claimed. Each relationship of claimed inventions should be similarly treated and the reasons for the conclusions of distinctness or independence set forth.") "The examiner must provide a clear and detailed record of the restriction requirement to provide a clear demarcation between restricted inventions so that it can be determined whether inventions claimed in a continuing application are consonant with the restriction requirement and therefore subject to the prohibition against double patenting rejections under 35 U.S.C. 121." (MPEP 814)

B. The current restriction is improper on its face

The examiner has failed to provide a clear and detailed demarcation between restriction groups. This is self-evident from comparison of, e.g., groups III and IV, which are described in *exactly the same way* ("a method of inhibiting neoplastic cell growth in a mammalian subject"). Additionally, the examiner has indicated that claims 55 and 58-60 are in both Groups. It is unclear how claims can be distinct from themselves, especially when the alleged demarcation is not a demarcation. It should be noted that Groups III and IV are also classified in the same class/subclass as the elected Group.

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There are many other examples of allegedly distinct groups which, while defined by slightly varying words, are equally difficult to separate by any lines of "clear demarcation." (See, for example, the aforementioned Groups III and IV, compared to, e.g., Group VI, which is directed to a method for treating a neoplastic disorder, or Group XII, directed to a method of inhibiting neoplastic cell growth in a human, or Group XIII, directed to a method of inhibiting neoplastic cell growth in a mammalian subject.) It will be readily apparent that a claim to treating a neoplastic disorder in a human could fall within all of these groups (humans are mammals), and other groups, and it would be impossible to properly assign such a claim to one group.

A related, fundamental defect with the restriction is a total failure to provide reasons for restriction. Instead of explaining how any single group is distinct from any other group, as directed by the MPEP, the restriction merely contains a one sentence conclusion ("The methods of groups I-XIII can be shown to be distinct as they each have different starting materials, method steps, and/or goals.") This is precisely the conclusory treatment of that is prohibited by the MPEP, as quoted above.

It appears that the actual basis for restriction was whether one claim was dependent from another or independent. However, there is no justification, in the provisions for analyzing patentable distinctness, for such a mechanical analysis.

Because the Patent Office has failed to provide demarcations between the groups or explain how the groups are allegedly distinct from each other, the restriction requirement is improper, and moreover, it is exceedingly difficult to traverse on the merits. (One cannot rebut a *prima facie* case that has not been set forth.) Notwithstanding, the Applicants identify some of the other reasons for removing the restriction requirement below.

C. Relatedness of all other groups to elected Group X

Group X is directed to "a method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase in blood vessels. Independent claim 81 in that group includes a step of administering to a mammalian organism (having a disease characterized by expression of Flt4 in blood vessels)

a composition that comprises an inhibitor of the binding between Flt4 and an Flt4 ligand. A Markush group of five classes of inhibitors is recited in the claim.

All of the other groups have varying degrees of relatedness to Group X and its claims. For example, antagonizing or inhibiting Flt4 function is a recurrent theme in the groups. Administering an inhibitor of the binding between Flt4 and its ligands is a recurrent theme in the groups. The Markush group of inhibitors recited in claim 81 is a recurrent theme in the claims of multiple groups. Flt4 expression in blood vessels (in the organism to be treated), and more particularly in the endothelia of the blood vessels, is a recurrent theme in multiple groups. The existence of neoplastic cell growth or a neoplastic disorder generally, or a breast carcinoma specifically, is a recurrent theme in multiple groups.

In order for any restriction to be maintained, it is incumbent upon the Patent Office to identify clear lines of demarcation between the groups, notwithstanding their relatedness, and define groups that maintain such demarcation. Moreover, demarcation alone is insufficient. The Patent Office also must provide reasons for concluding that the groups, so demarked, are distinct.

In the event that such restriction is imposed, the Applicants request that it be made non-final, to permit a traversal of the reasons for restriction.

D. No serious burden

Moreover, applicants request that the restriction requirement be reconsidered because the examiner has not shown that a serious burden would be required to examine all of the claims. M.P.E.P. § 803 provides, "If the search and examination of an application can be made without serious burden, the Examiner **must** examine it on the merits, even though it includes claims to distinct or independent inventions." *(Emphasis added.)* Even a *prima facie* showing of burden (e.g., by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 803.02, can be rebutted by appropriate showings or evidence by the applicant.

There would be no serious burden examining all of the claims in this application at one time. Compelling evidence of this is the fact that the prior examiner

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examined similar claims (and more claims) to the point of allowance in the parent application. (See Remarks section of the Applicant's preliminary amendment in this case, which correlates pending claims in this case with claims that were examined and allowed in USSN 09/169,079.) The current claims (which contain limitations relating to blood vessel expression of Flt4), are believed to be entitled to a longer patent term than the claims which were permitted to issue in the parent case, by virtue of a later priority claim. However, these claims do not pose a serious burden of examination in one application. Moreover, the relatedness, discussed above, indicates that the search for each method claims will be similar.

Likewise, the allowed claims in the parent application contain limitations directed to a variety of different Flt4 inhibitors. No serious burden was found in examining claims that recite more than one inhibitor – the second "subgroup" (A-E) prong of the restriction requirement.

Conclusion

For the foregoing reasons, applicants request reconsideration and withdrawal of the restriction requirement. Should the examiner have any questions or comments regarding this response or the application, the examiner is invited to contact the undersigned agent or David A. Gass, attorney for applicants, at the number indicated below.

Dated: October 17, 2006

Respectfully submitted,

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